

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

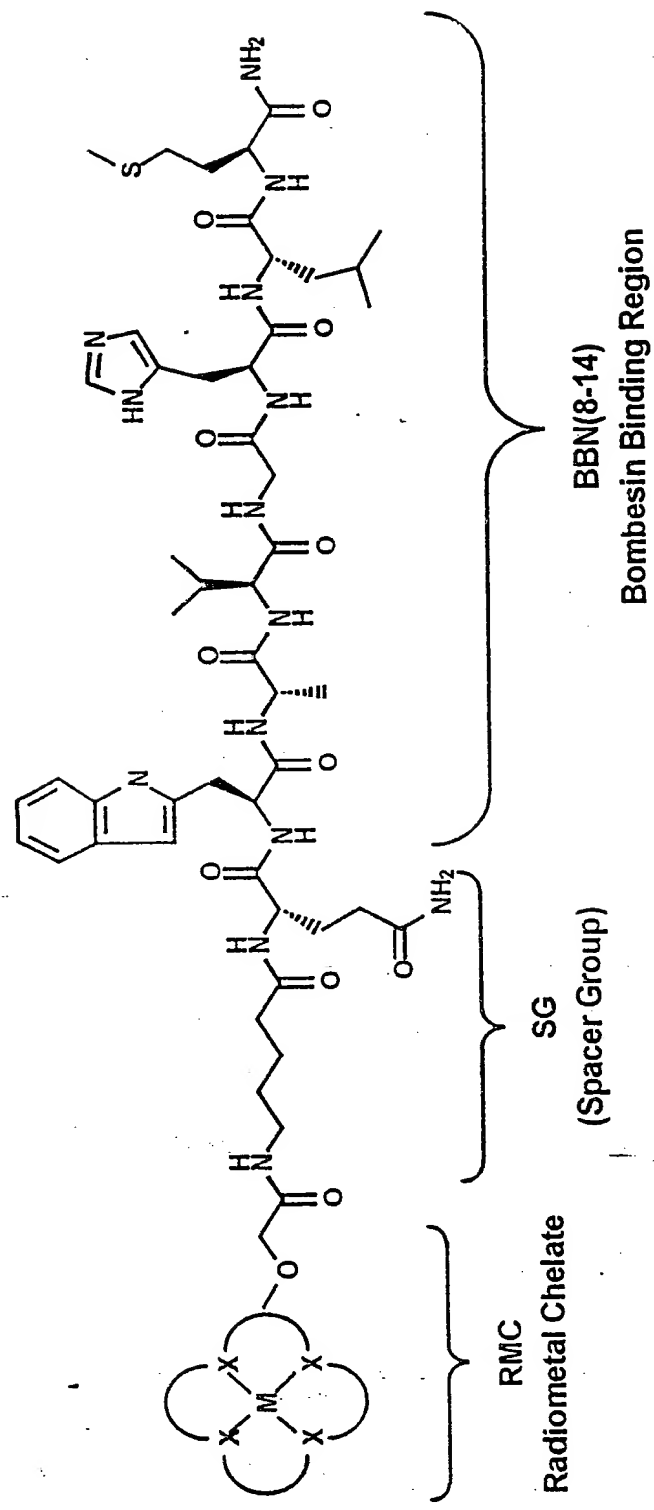
Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

Radiometal Conjugate

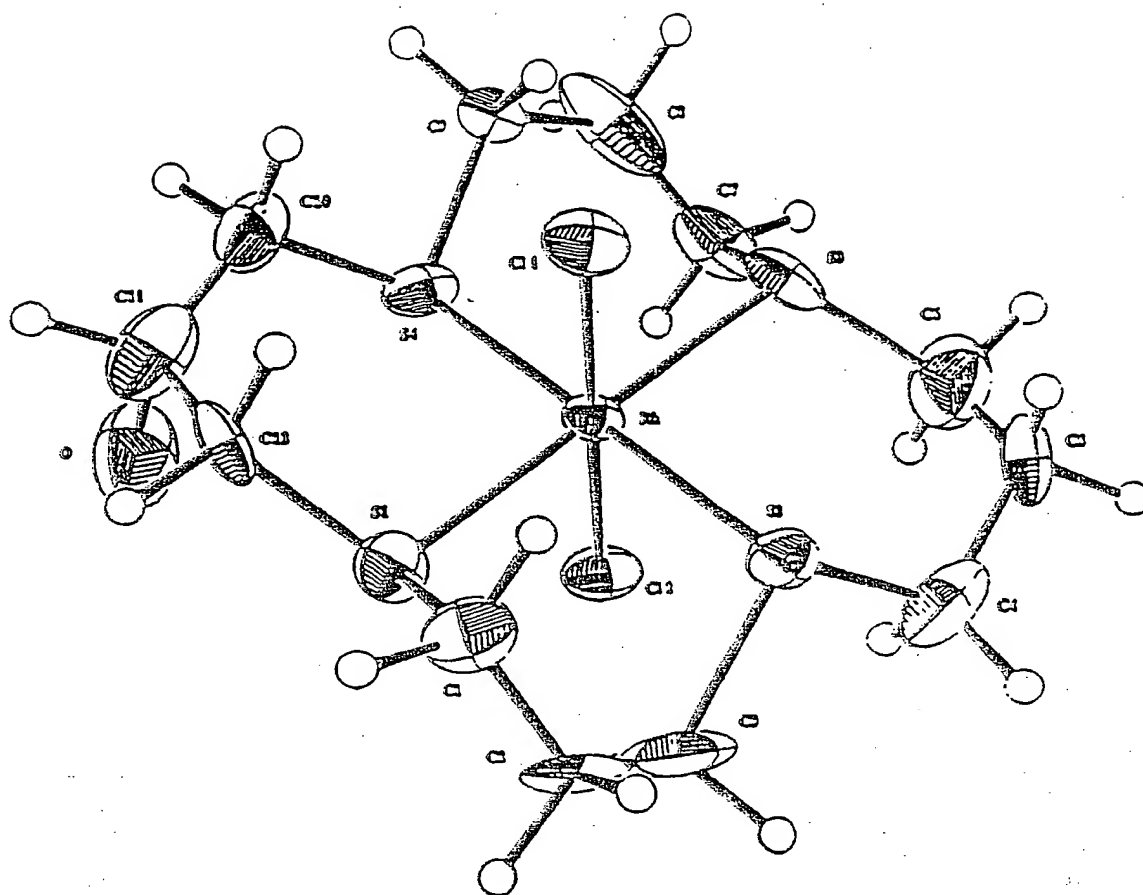


Radiometal conjugate of a BBN analogue that has high affinity for GRP receptors.

RMC=Radiometal chelate, where $M = {}^{99m}\text{Tc}$, ${}^{186/188}\text{Re}$, ${}^{105}\text{Rh}$ and X =chelating atoms.

SG=Spacer group or linker that covalently attaches the chelate to the N-terminal end of the BBN binding region (BBN_{BR})

Figure 1



ORTEP Drawing of $\{Rh[16]aneS_3-olCl_2\}^+$

Figure 2

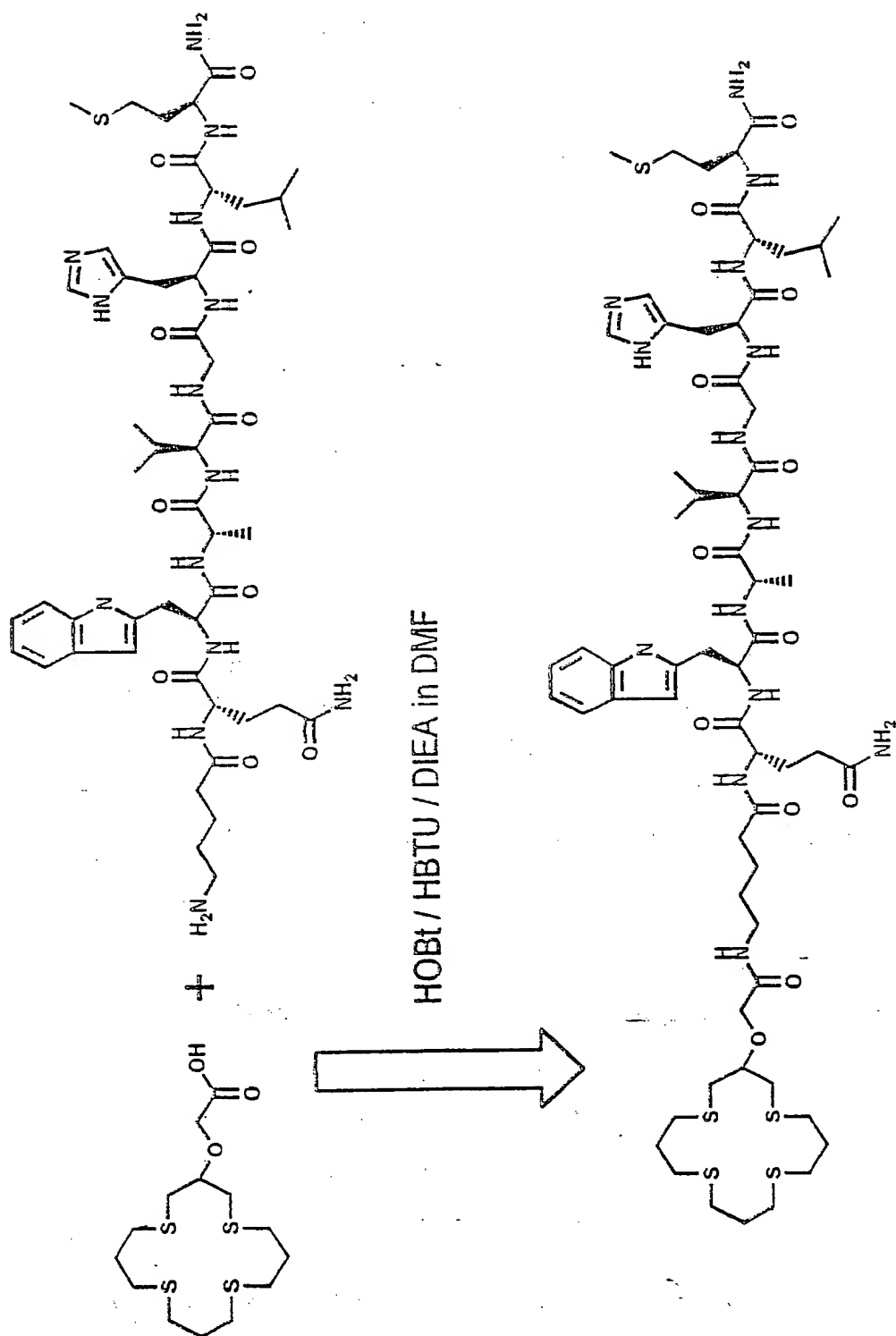


Figure 4

mIP-Lys³-BOMBESIN

Iodinated Bombesin Analogues

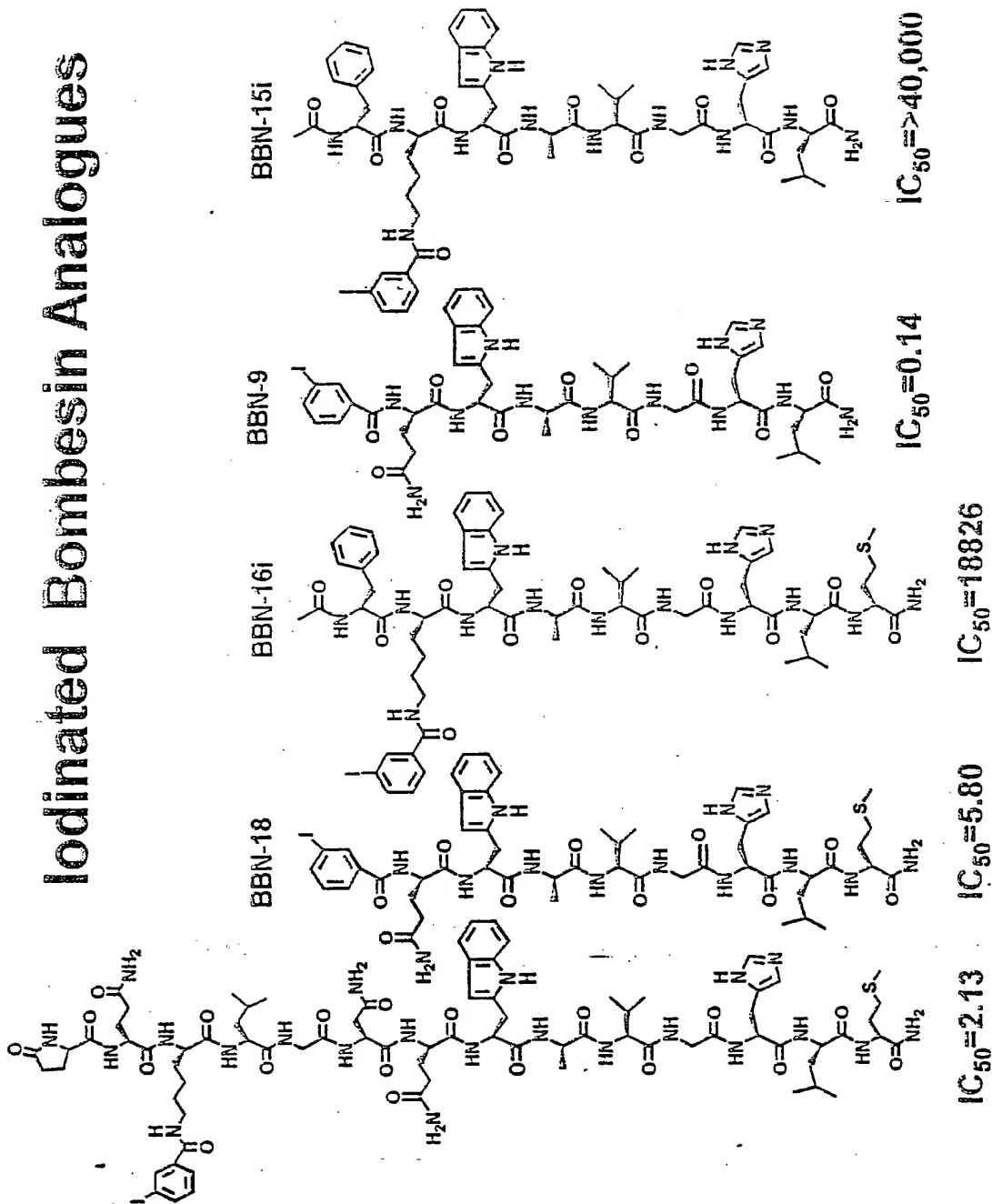


Figure 5

Tethered Bombesin Analogues

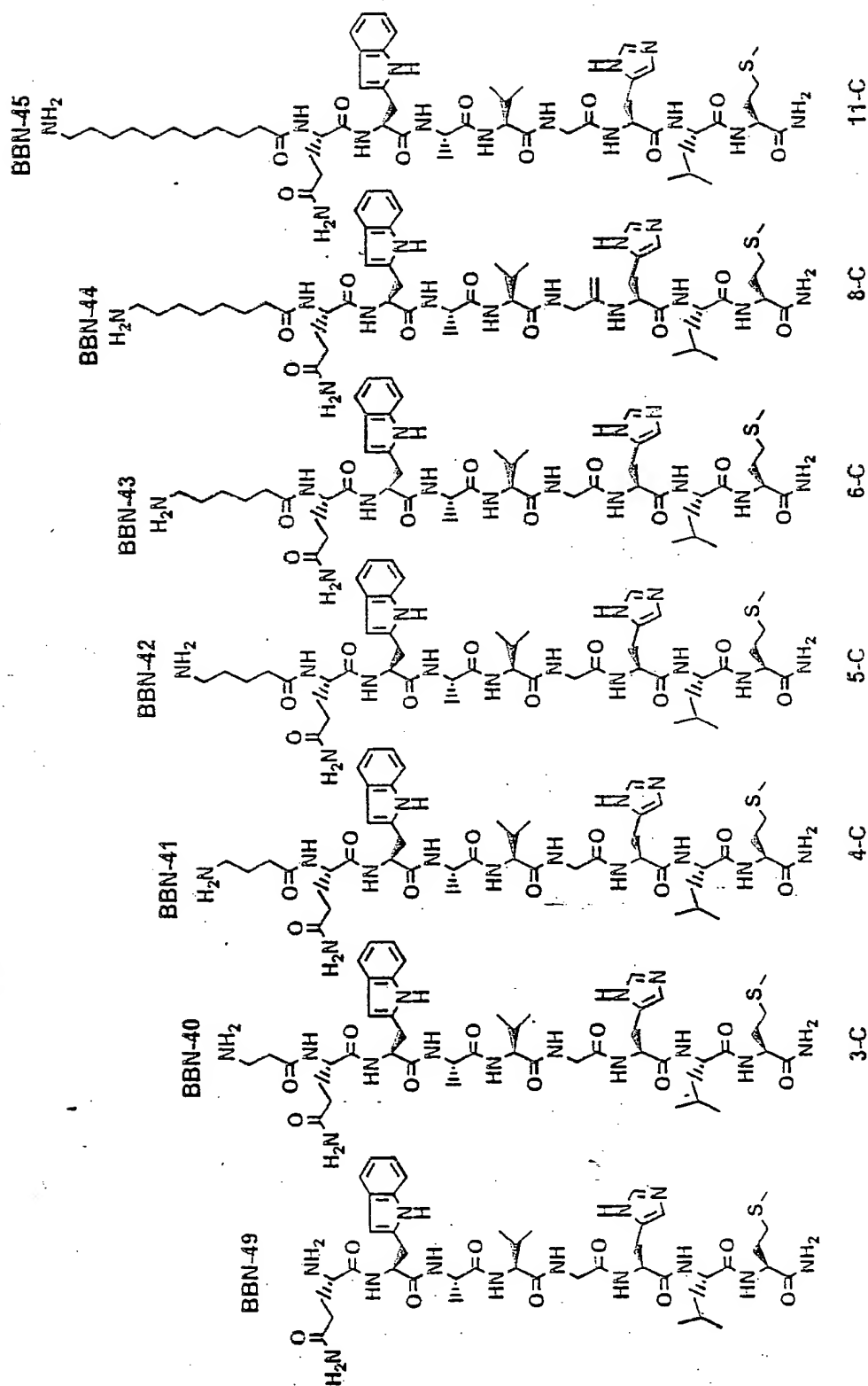


Figure 6

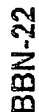
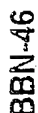
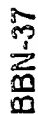
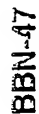
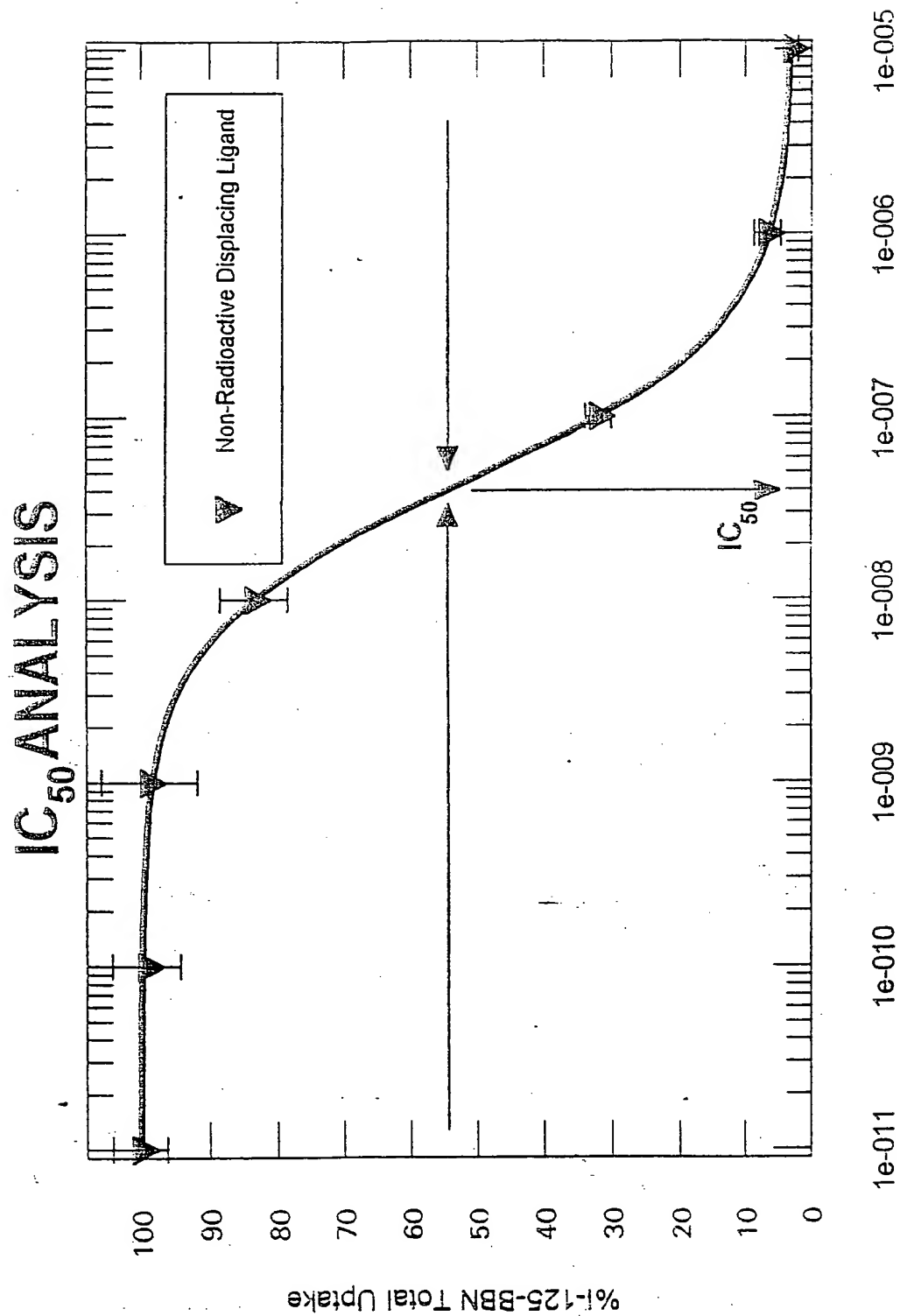
[illegible]

Figure 7

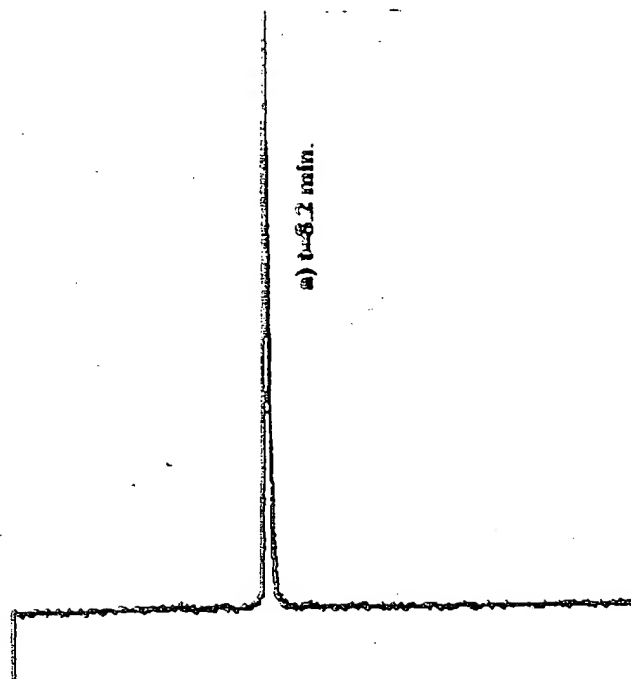


Molar Concentration of Displacing Ligand

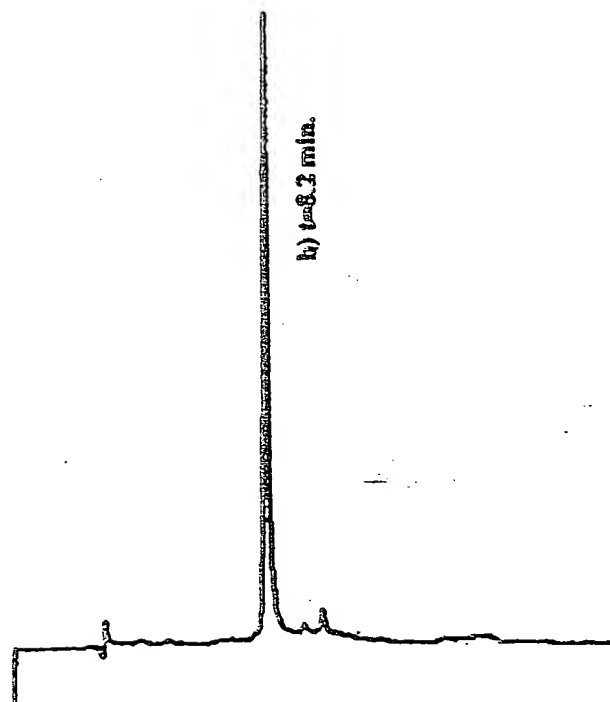
Figure 8



A.



B.



HPLC Chromatogram of Rhodium-BBN-37
Top: $^{105}\text{RhCl}_2\text{-BBN-37}$
Bottom: $\text{RhCl}_2\text{-BBN-37}$

Figure 10

^{125}I -Tyr⁴-Bombesin Internalization **Efflux in ^{125}I -Tyr⁴-BBN Free Buffer**

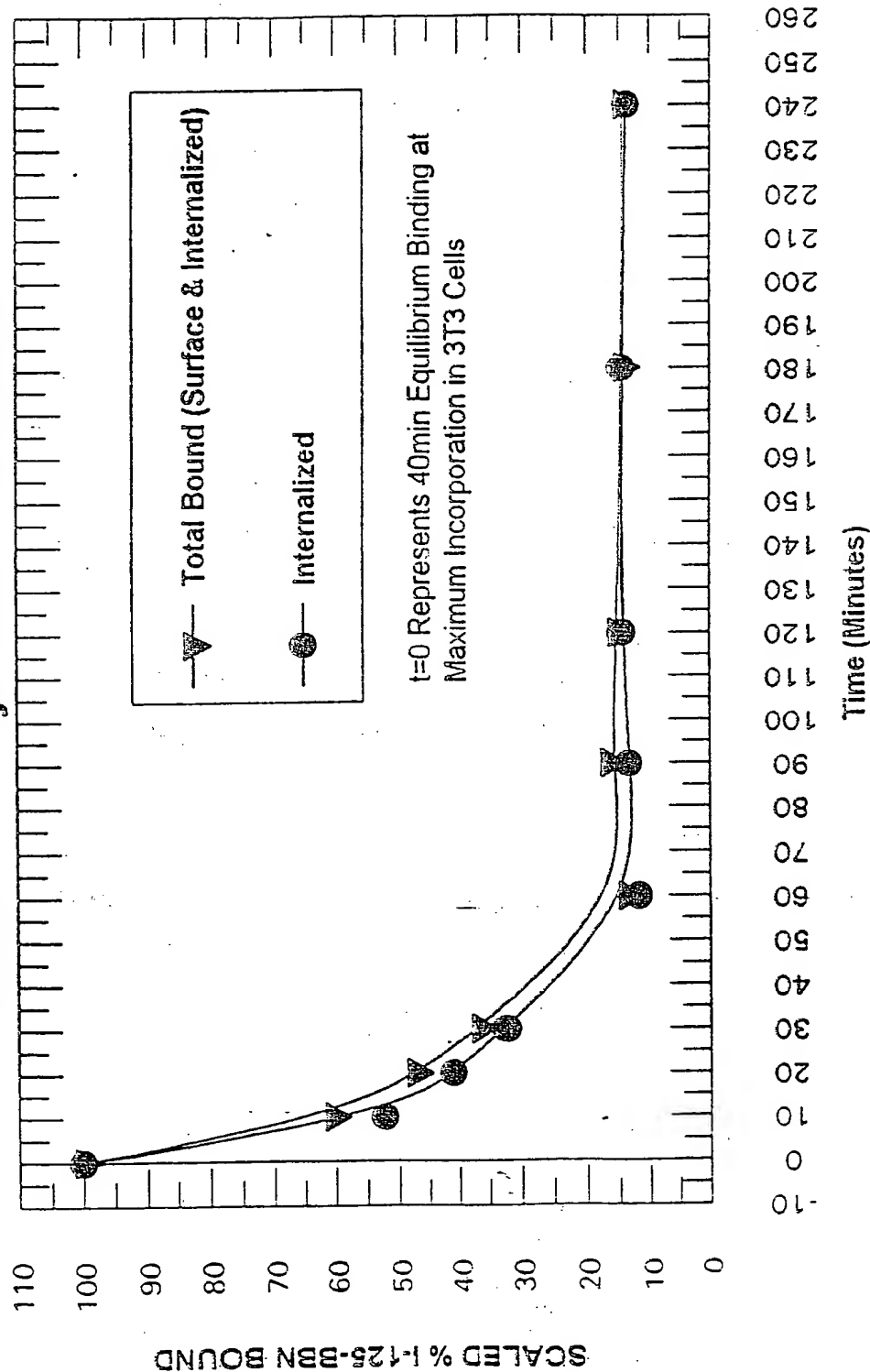


Figure 11

I-125 Bombesin Internalization Efflux in I-125 Free Buffer

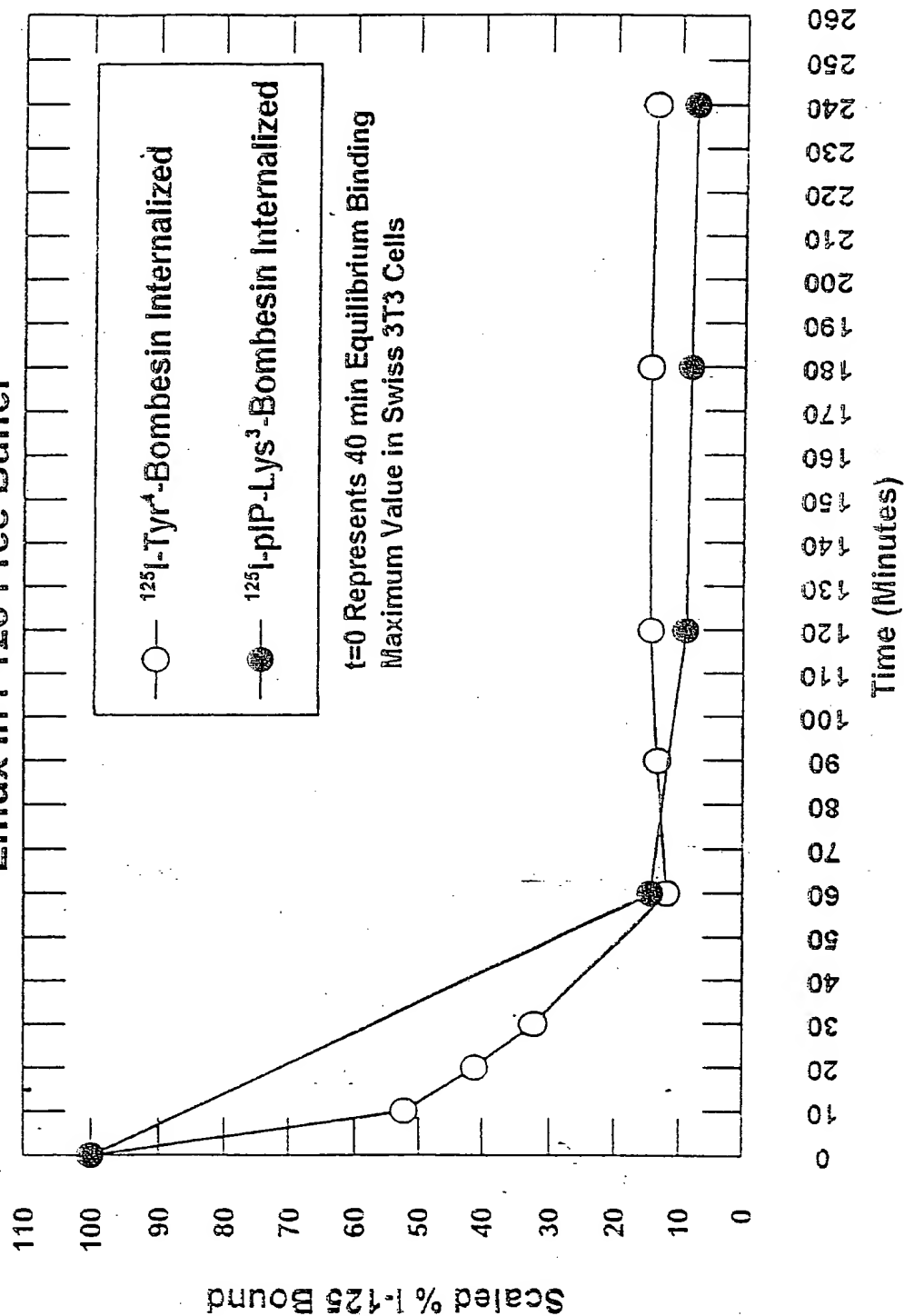
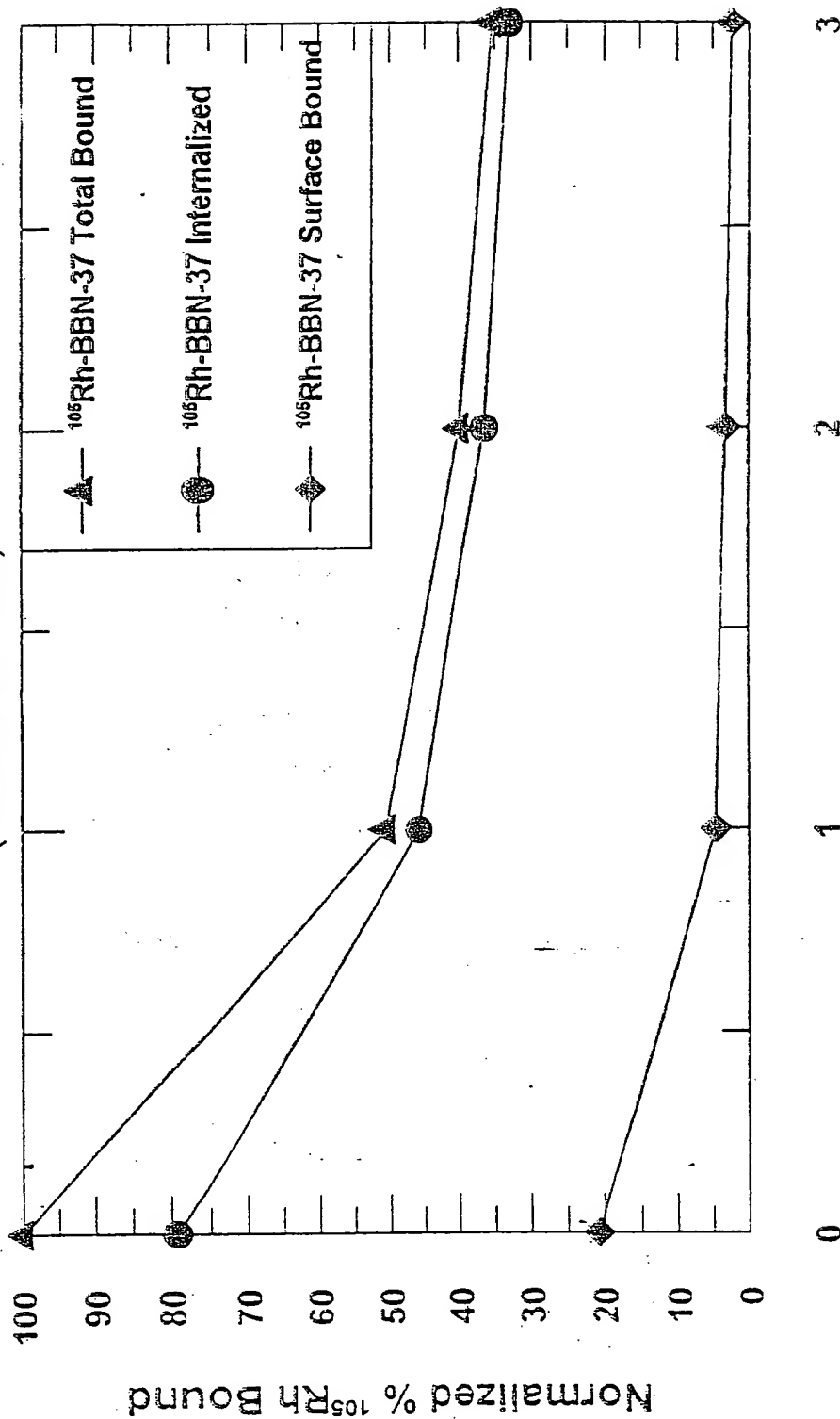


Figure 12

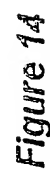
Efflux of ^{105}Rh -BBN-37 in Swiss 3T3 Cells

(Normalized Data)



Time (Hours)

Figure 13



^{105}Rh -BBN-61 Efflux Evaluation Swiss 3T3 Cell Evaluation

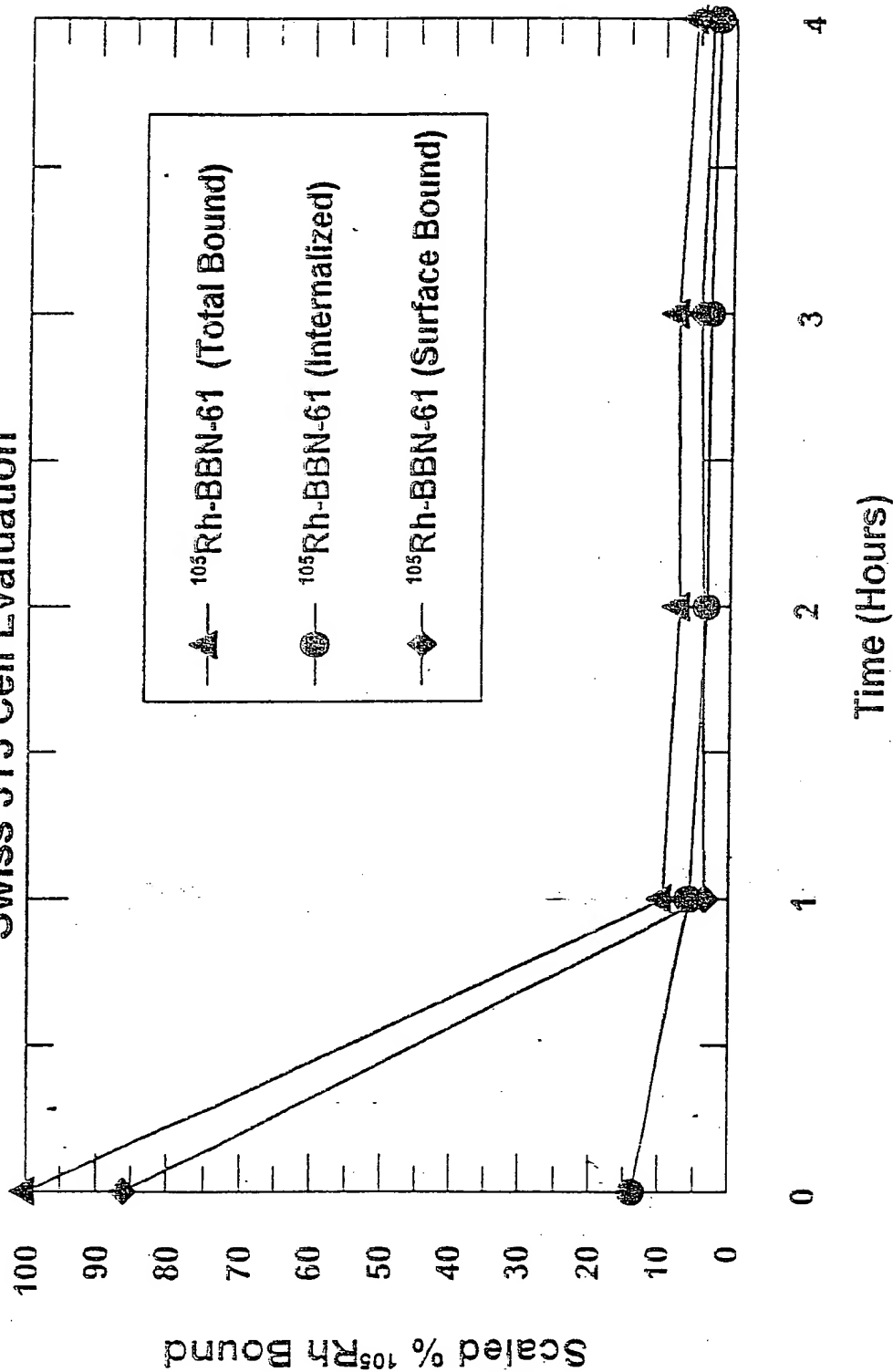


Figure 15

Efflux of ^{105}Rh -BBN-22 vs. ^{105}Rh -BBN-37 in Swiss 3T3 Cells (Non-Normalized Data)

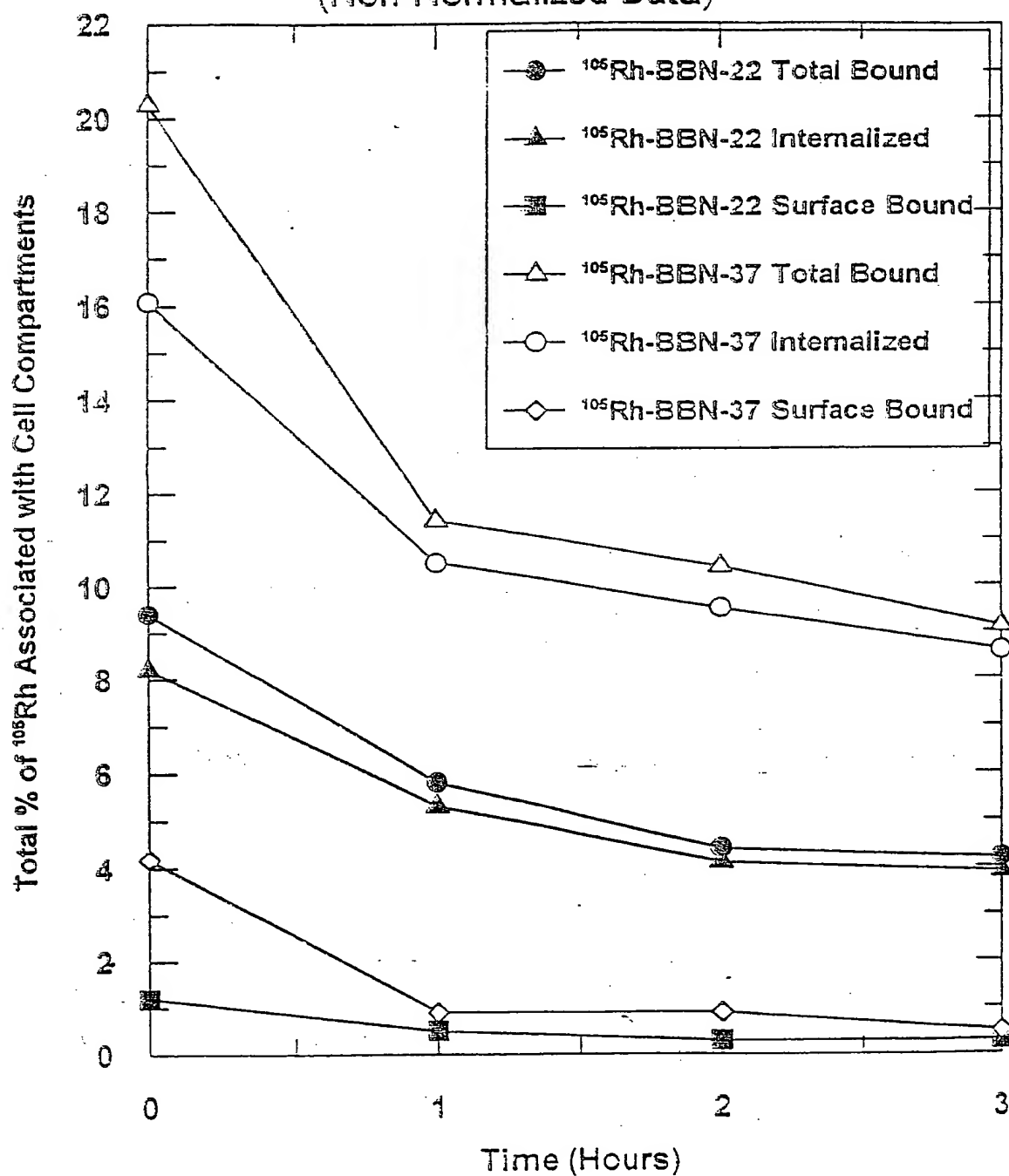
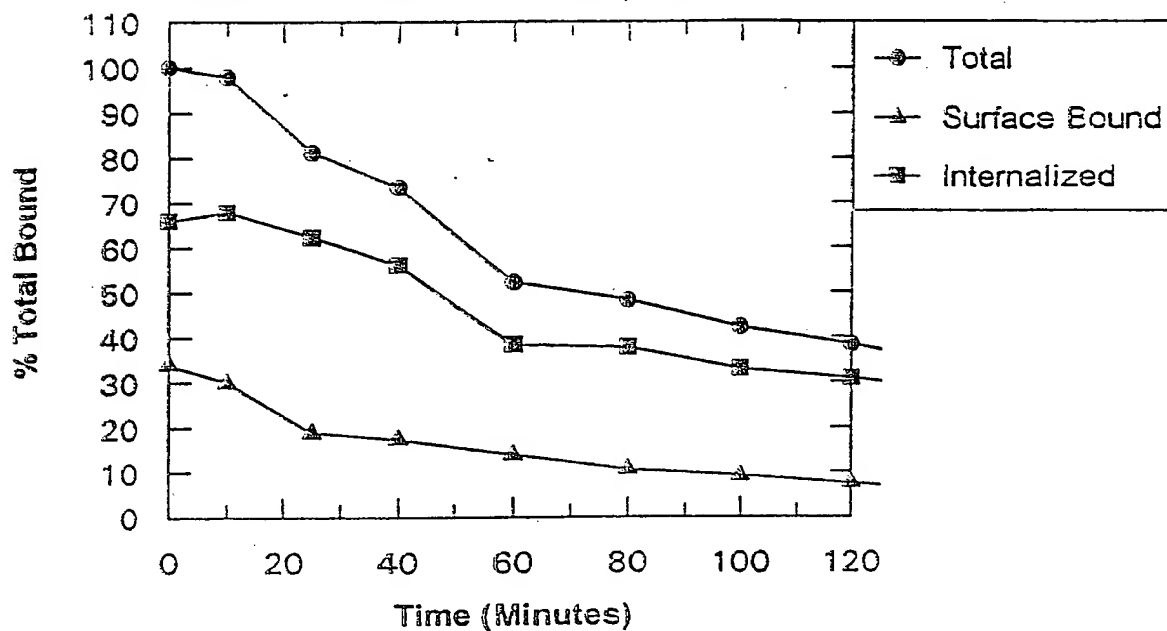


Figure 16

Pancreatic CA Cell Binding

A.

Efflux of ^{125}I -Tyr¹-BBN from CF PAC1 Cells



B.

Efflux of ^{105}Rh -BBN-37 from CF PAC1 Cells

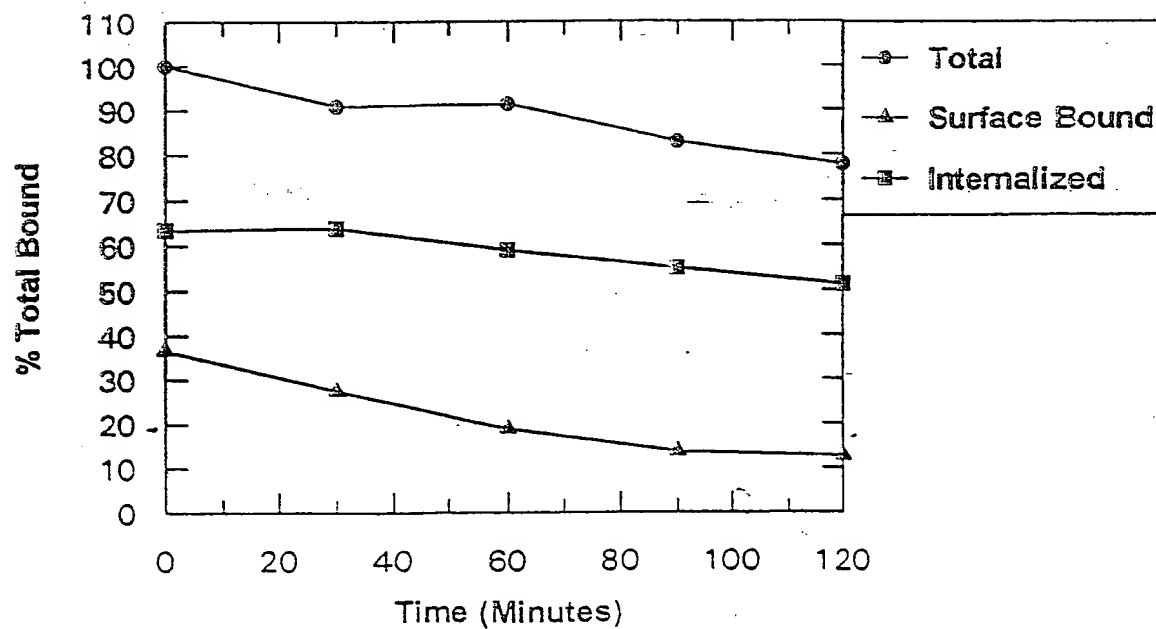
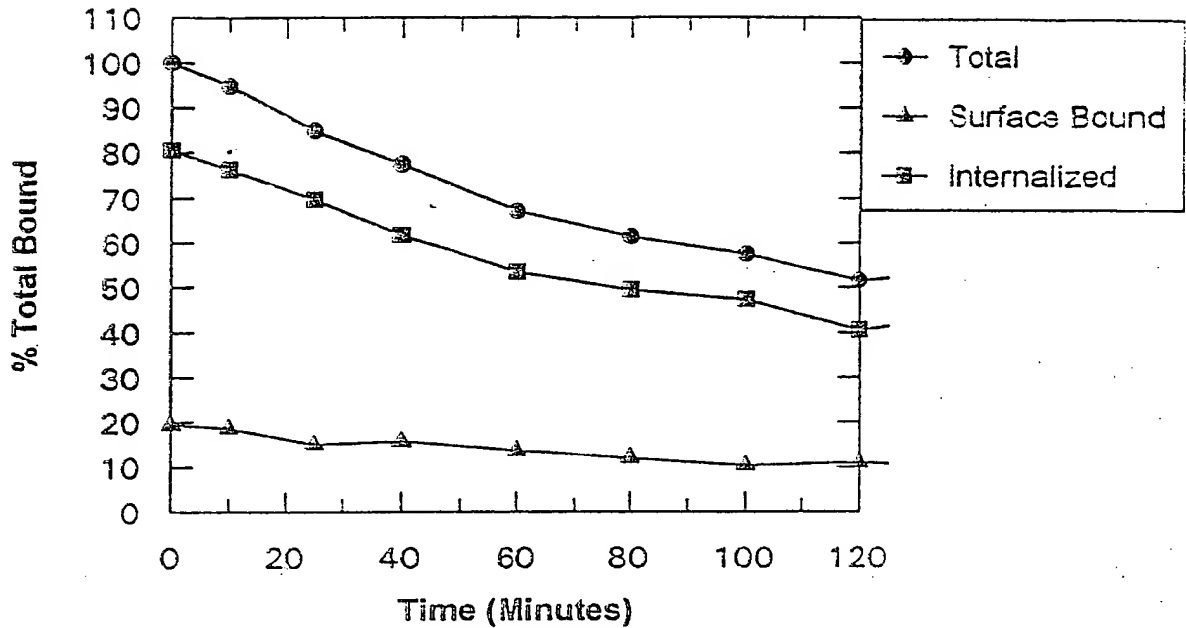


Figure 17

Prostate CA Cell Binding

A.

Efflux of ^{125}I -Tyr¹-BBN from PC-3 Cells



B.

Efflux of ^{105}Rh -BBN-37 from PC-3 Cells

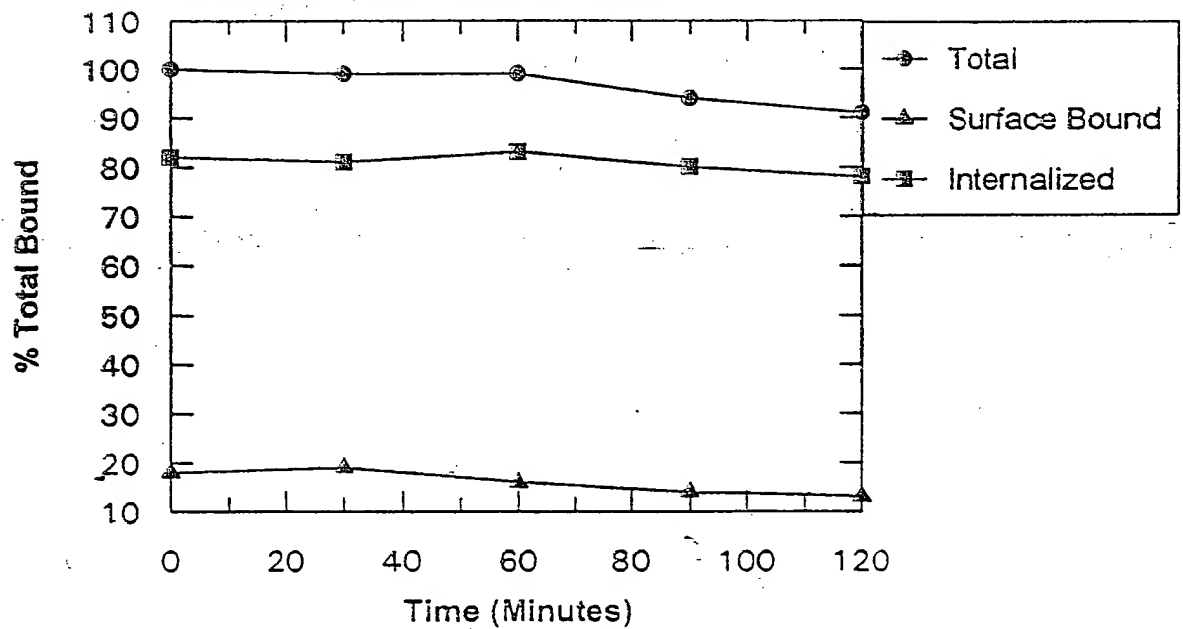
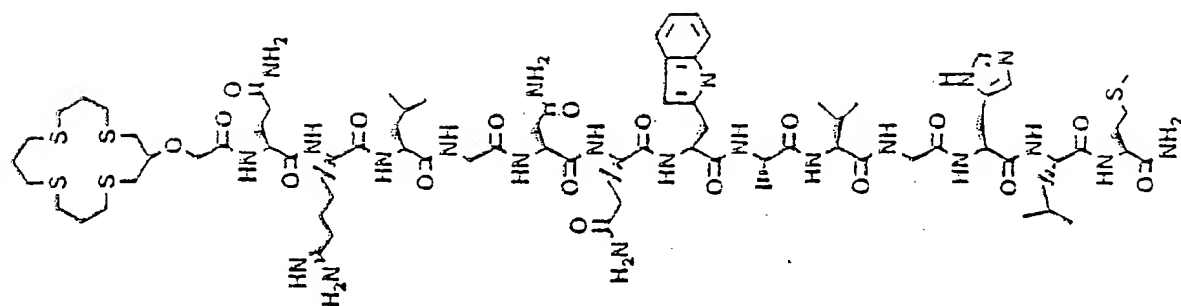


Figure 18

[16]aneS₄ Bombesin Analogues

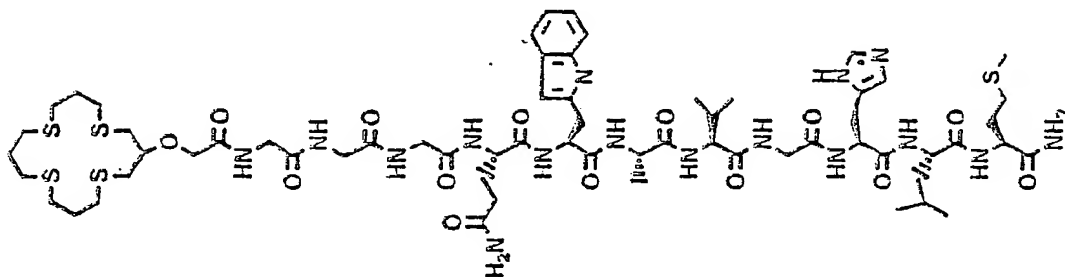
BBN-101



IC₅₀(nM)

1.2 ± 0.7
2.1 ± 0.5
2.4 ± 0.9

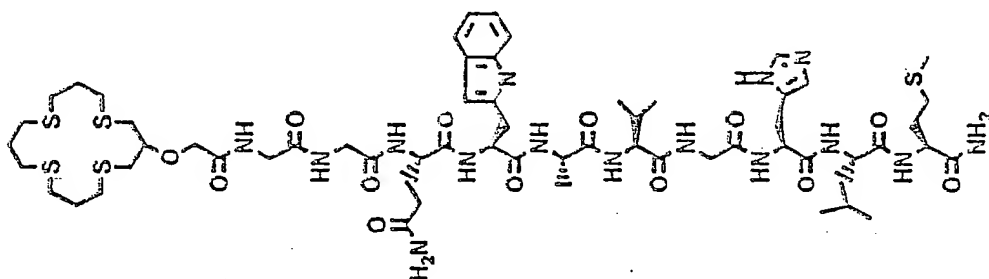
BBN-97



IC₅₀(nM)

38.0 ± 11.7
6.9 ± 2.8
14.2 ± 6.8

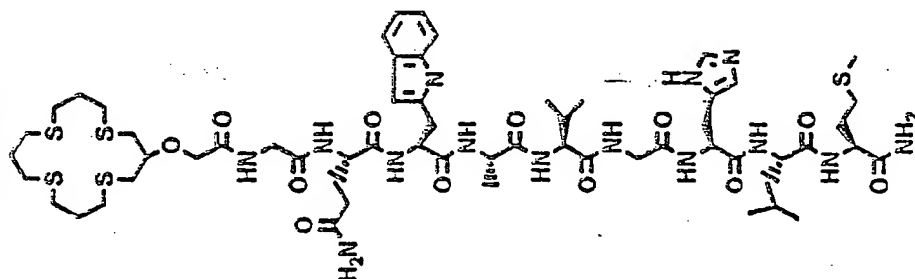
BBN-98



IC₅₀(nM)

3.3 ± 0.2
4.3 ± 2.2
6.1 ± 3.3

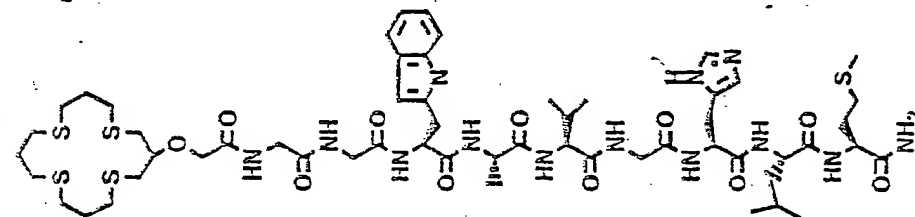
BBN-99



IC₅₀ (nM)

6.0 ± 0.5
3.3 ± 1.9
4.8 ± 0.8

BBN-96



IC₅₀ (nM)

18.4 ± 4.5
8.8 ± 1.8
39.5 ± 10.7

Swiss 3T3
PC-3
CF PAC-1

FIGURE 19

Rhodium-[16]aneS₄ Bombesin Analogues

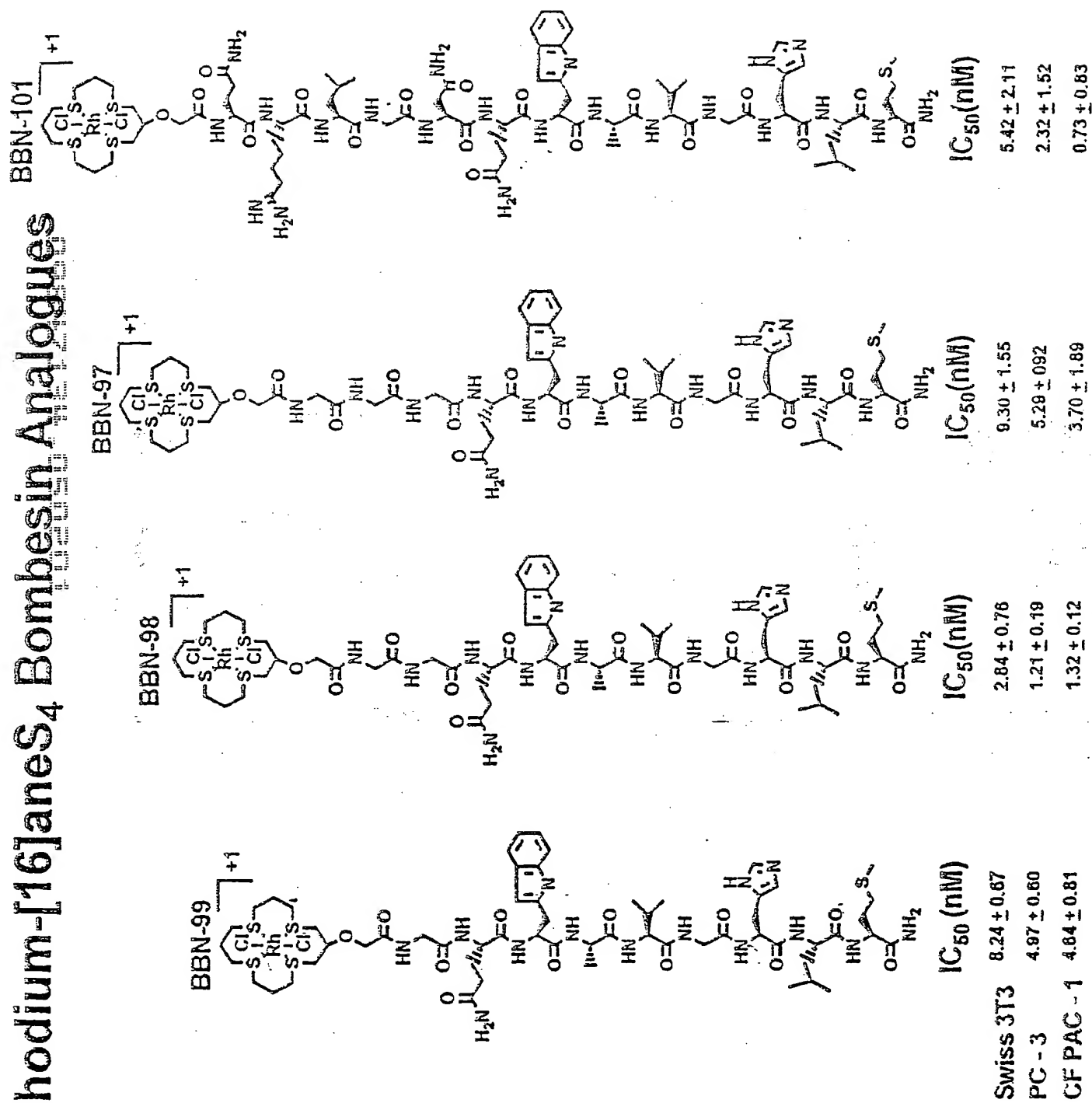


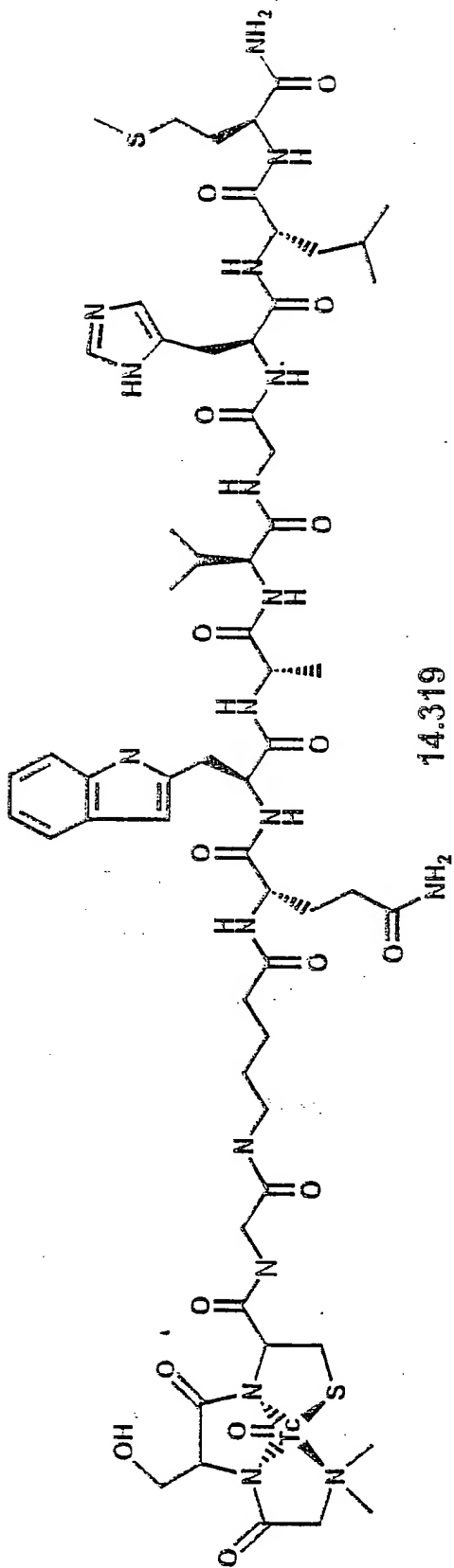
FIGURE 20

[illegible][illegible]CN(C)CC(=O)NC(=O)CSCC(=O)NCCCCCN(CCCC(=O)N)C(=O)N[C@@H](Cc1c[nH]c2ccccc12)C(=O)N[C@H](C)[C@@H](C)C(=O)N[C@@H](C(C)C)C(=O)N[C@@H](Cc1c[nH]cn1)C(=O)N[C@@H](CS)C(=O)N

(7-14)-BBN-C

RP414-8C-BBN(7-14)

TOC-44444
99mTc-BBN-122



14.319

HPLC Gradient Elution Program

Flow 1.5 ml/min
Solvent A = H₂O with 0.1% TFA
Solvent B = CH₃CN with 0.1% TFA

time(min)	%A/%B
0	95/5
25	30/70
30	95/5

STOP

START

Figure 22

^{99m}Tc -BBN-122 Uptake in Human Prostate Cancer Cells

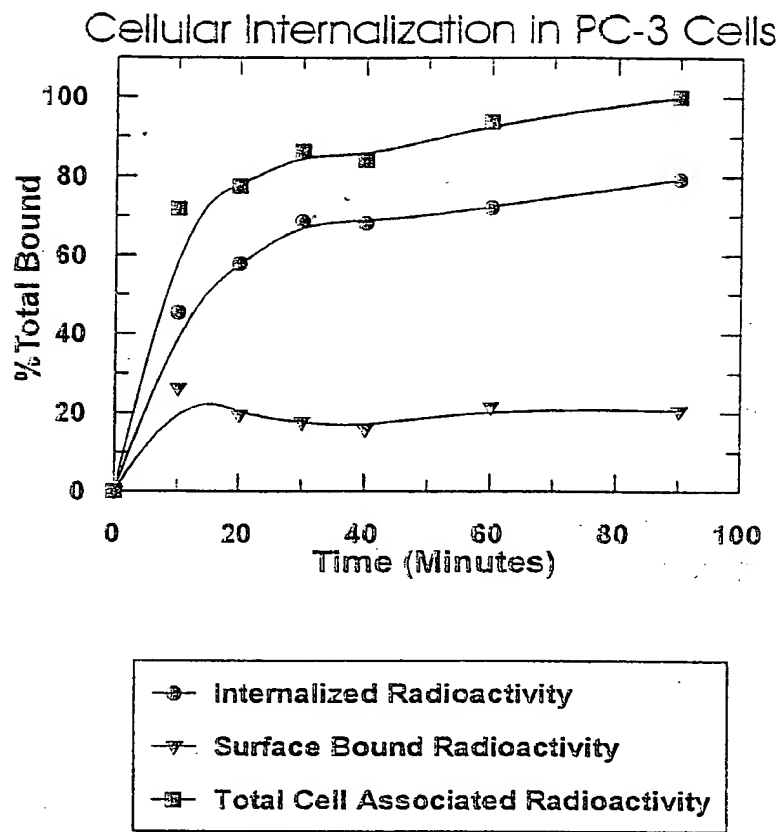


Figure 23

^{99m}Tc-BBN-122 Internalization in Human Pancreatic Cancer Cells

Cellular Internalization in CFPAC-1 Cells

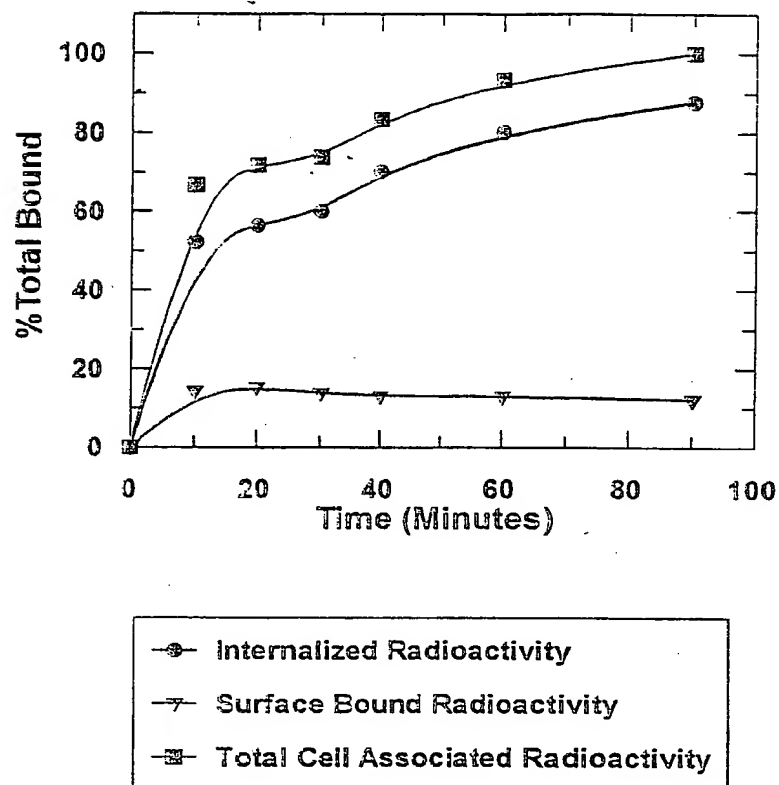


Figure 24

^{99m}Tc-BBN-122 Retention in Human Prostate Cancer Cells

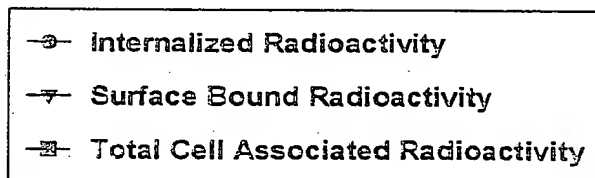
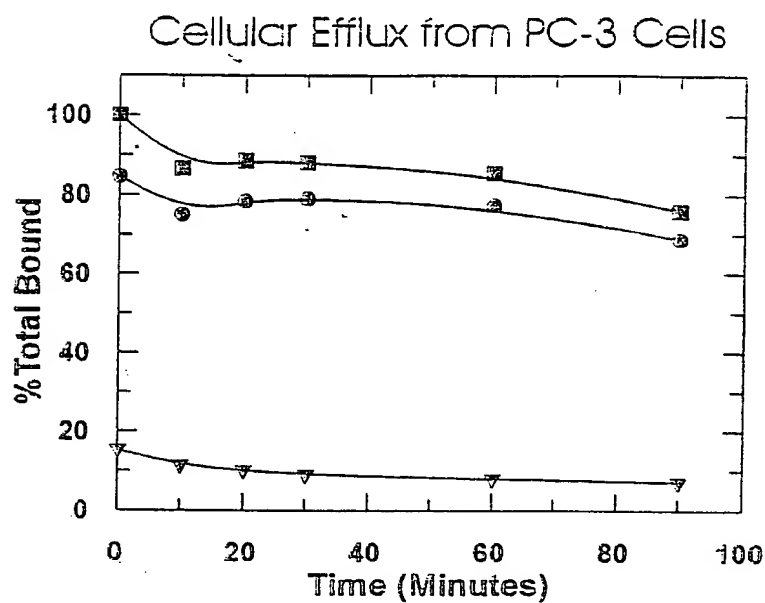


Figure 25

^{99m}Tc-BBN-122 Retention in Human Pancreatic Cancer Cells

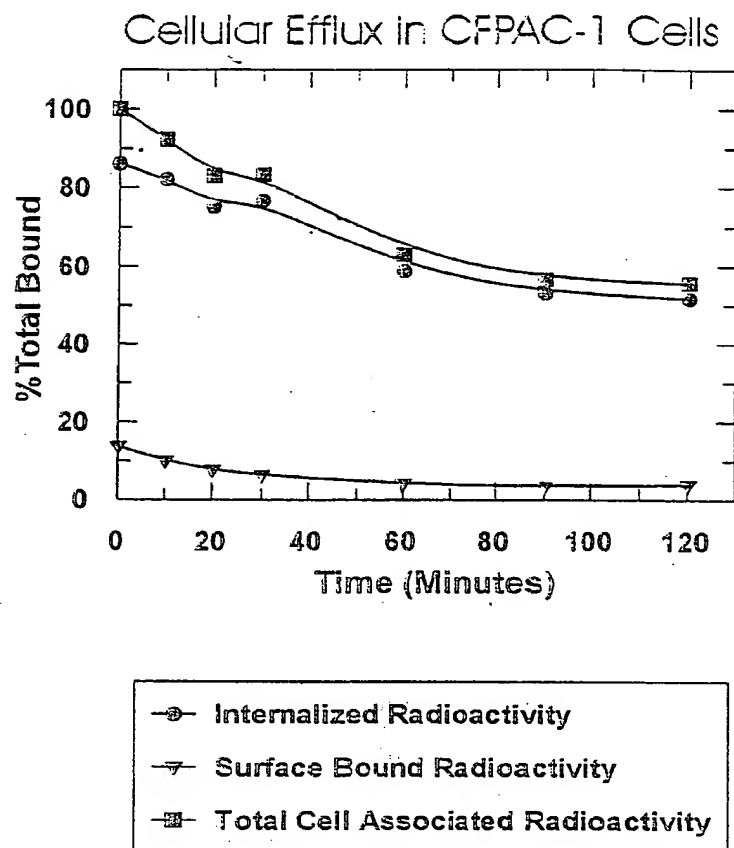


Figure 26

DOTA-BBN[7-14]NH₂ analogues.

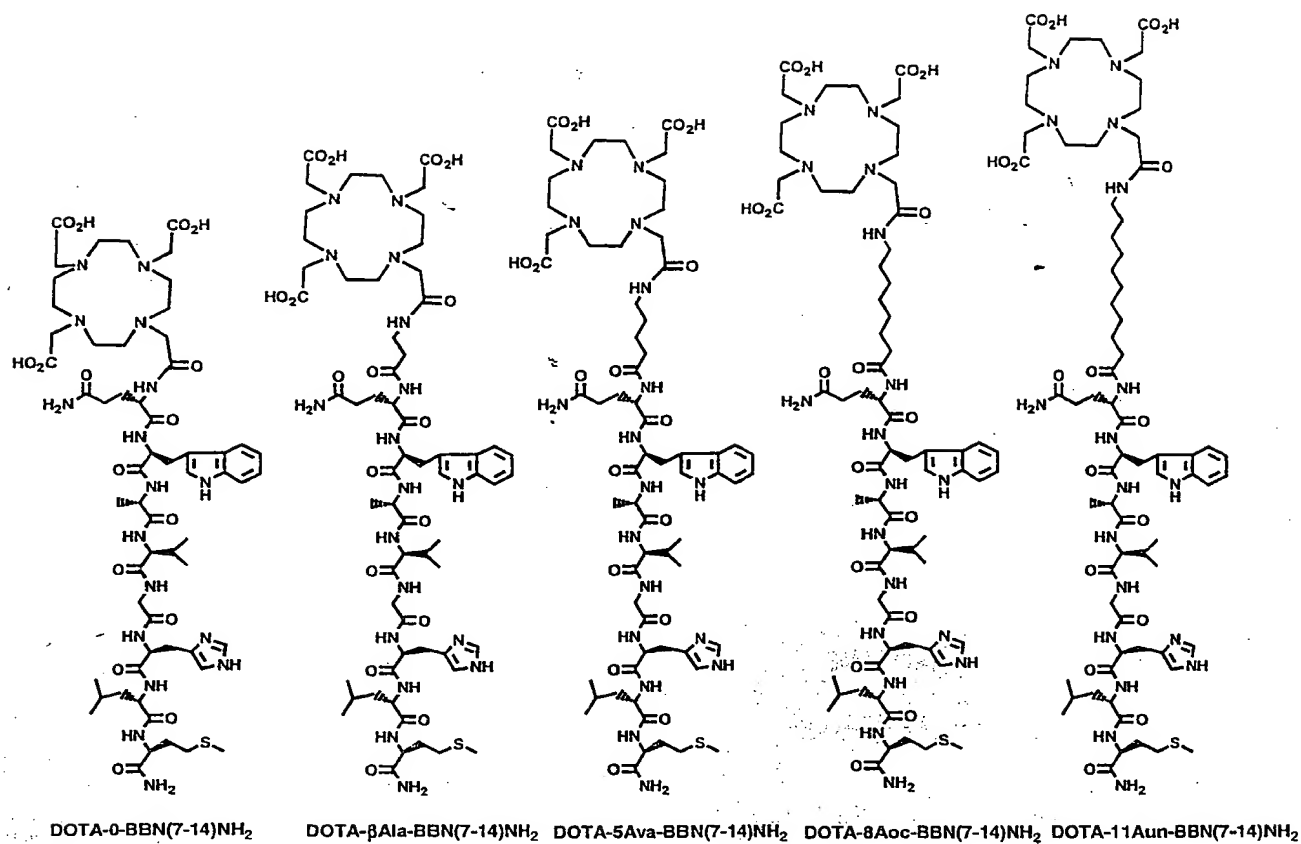


FIGURE 27

HPLC chromatograms of (a) DOTA-BBN[7-14]NH₂ ($\lambda = 280$ nm) (b) In-DOTA-BBN[7-14]NH₂ ($\lambda = 280$ nm) and (c) ¹¹¹In-DOTA-BBN[7-14]NH₂ (radiometric).

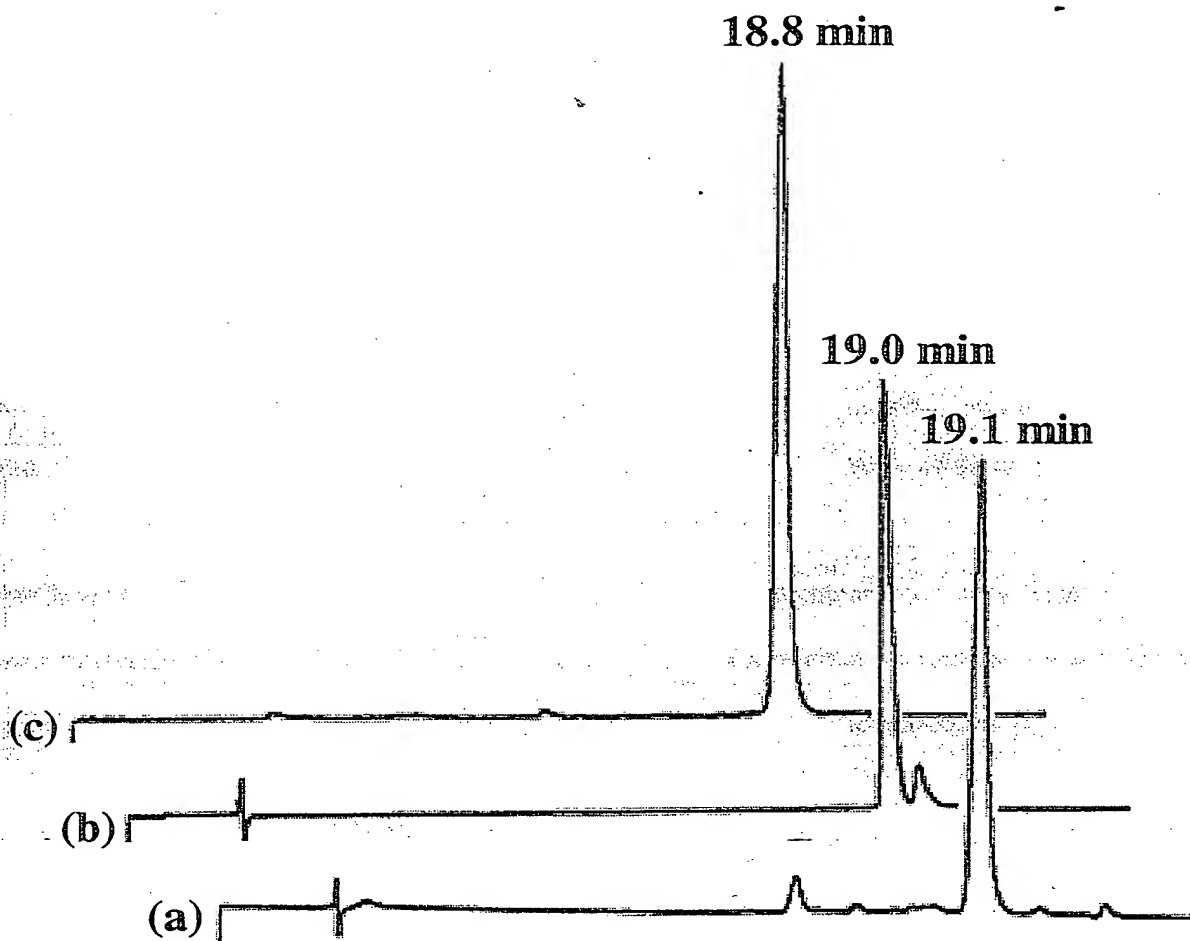


FIGURE 28

Competitive binding assay of In-DOTA-8-Aoc-BBN[7-14]NH₂ vs. ¹²⁵I-Tyr⁴-BBN in PC-3 cells.

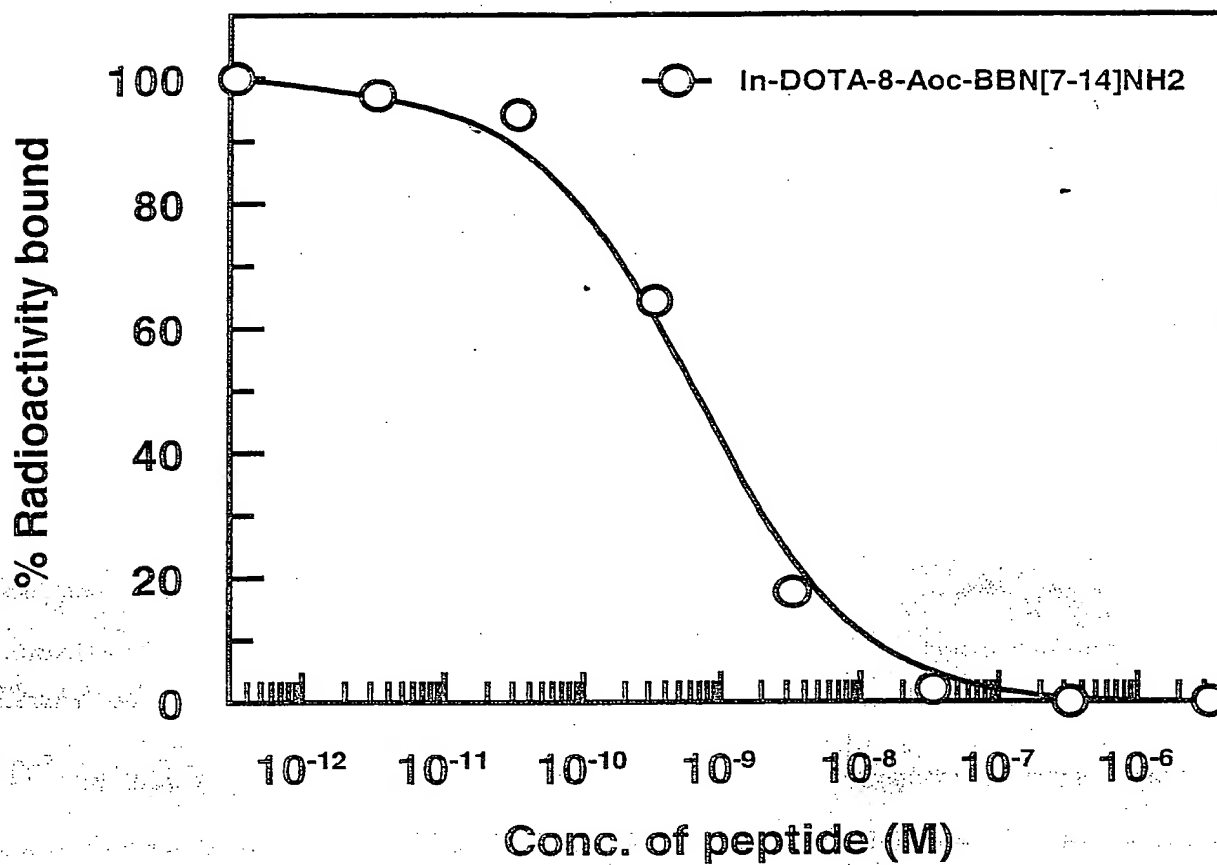


FIGURE 29

Internalization of ^{111}In -DOTA-8-Aoc-BBN[7-14] NH_2 in PC-3 cells.

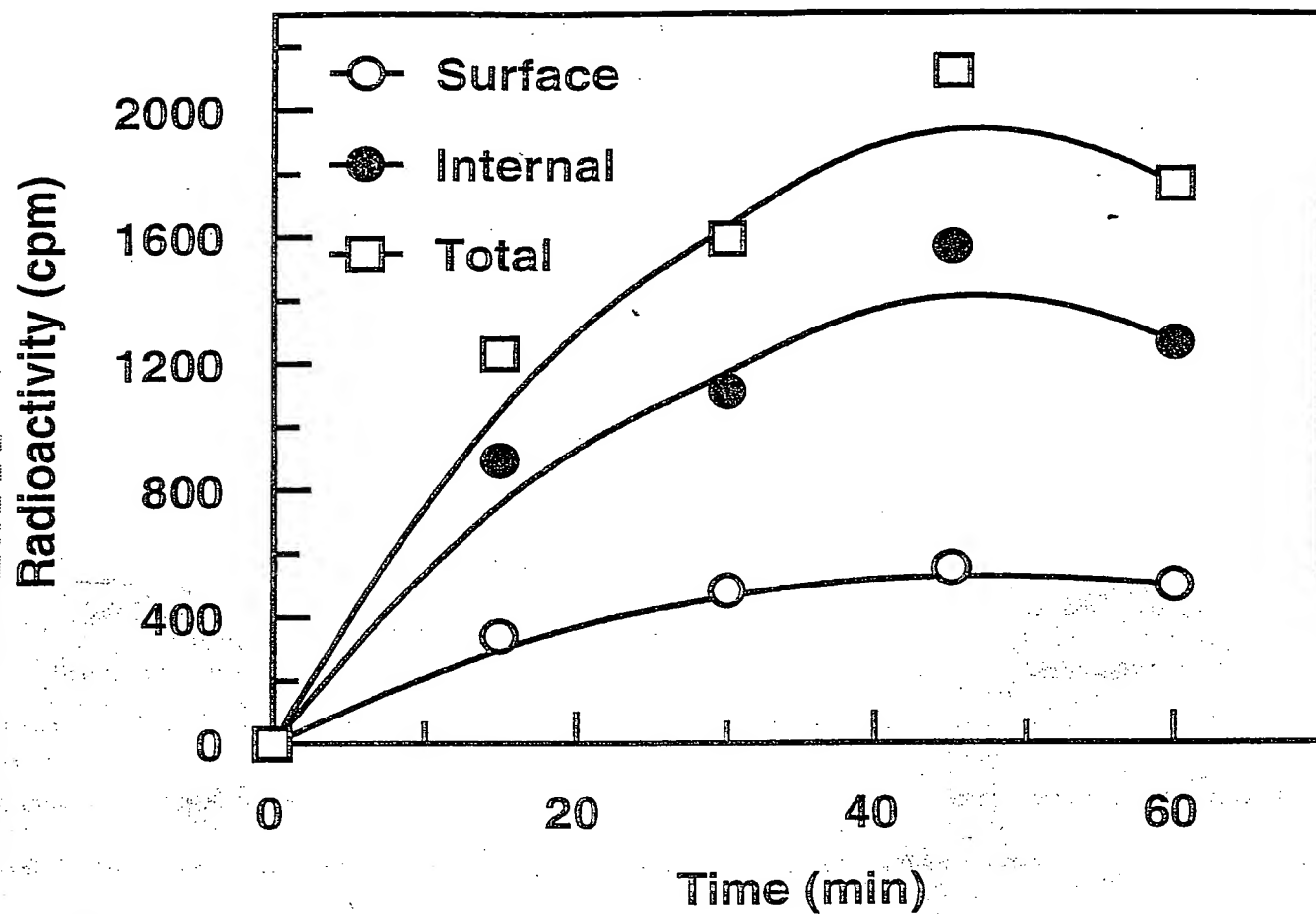


FIGURE 30

Efflux of ^{111}In -DOTA-8-Aoc-BBN[7-14] NH_2 in PC-3 cells.

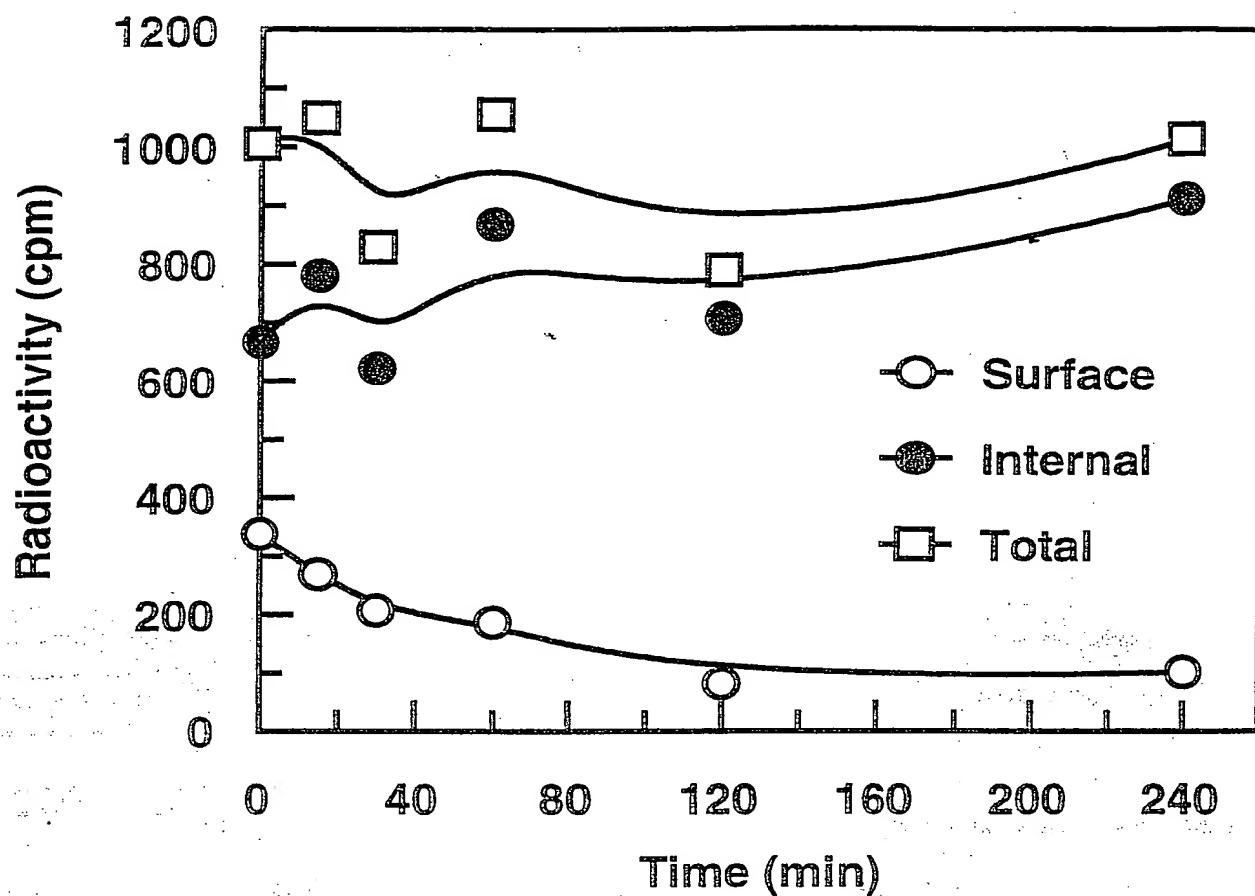


FIGURE 31

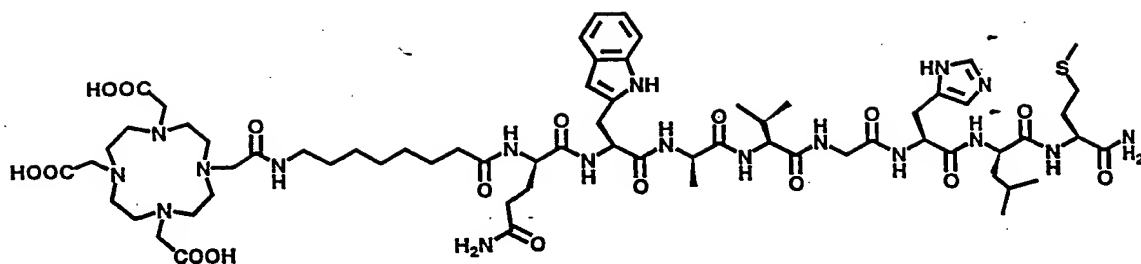


Figure 32